



# **Neuroscience module**

## **Lecture (5)**

### **Neurotransmitters related to depression, gait disorders and anxiety**

**BY**

**Dr. Fayda Elazazy**

**Professor of Medical Biochemistry  
and Molecular Biology**

# Lecture Key points



- Metabolism of neurotransmitters and related disorders



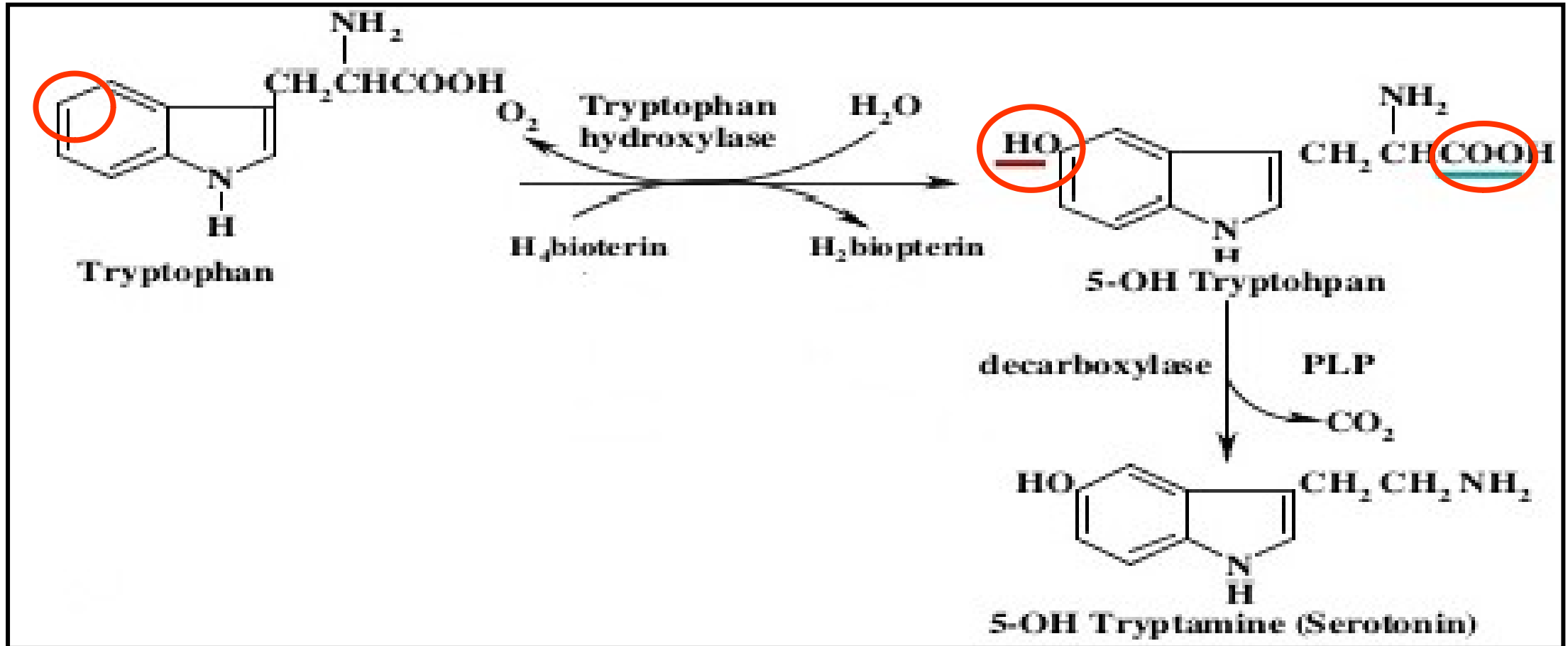
**By the end of this lecture the student will be able to:**

- 1. Define neurotransmitter**
- 2. Illustrate the major biochemical pathways for neurotransmitter synthesis and degradation.**
- 3. Relate some clinical disorders to disruption of neurotransmitter metabolism like:**
  - Carcinoid tumor (argentaaffinoma)**
  - Parkinson's Disease**
  - Pheochromocytoma**
  - Convulsions**

# Neurotransmitters

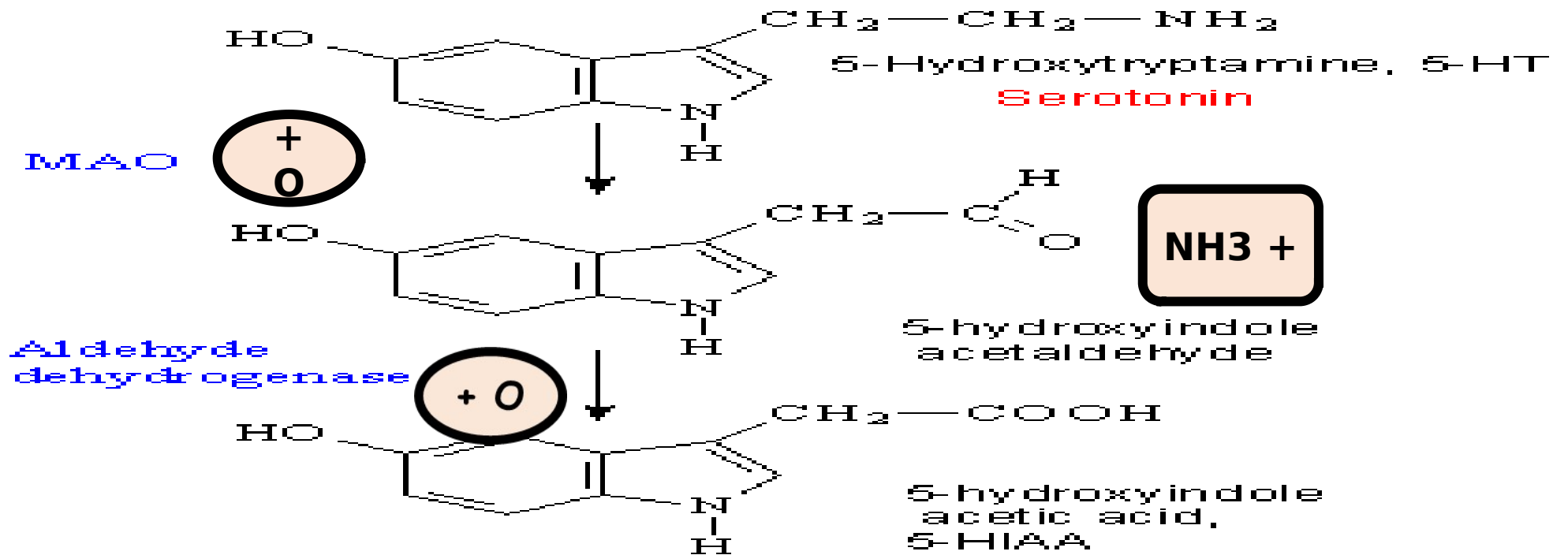
**Are the brain chemicals synthesized by nerve cells and communicate information throughout our brain and body cells**

# 1) Biosynthesis of Serotonin



[https://www.google.com/search?q=synthesis+of+serotonin&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjA6\\_Ho3e7IAhUCqXEKHRgrBwgQ\\_AUIEigB&biw=1366&bih=637](https://www.google.com/search?q=synthesis+of+serotonin&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjA6_Ho3e7IAhUCqXEKHRgrBwgQ_AUIEigB&biw=1366&bih=637)

# Degradation of Serotonin



## Serotonin Catabolism

Serotonin is **degraded** by monoamine oxidase enzyme (**MAO**) MAKE **OXIDATIVE DEAMINATION** producing 5-hydroxyindolacetic acid (**5-HIAA**).

[https://www.google.com/search?biw=1366&bih=637&tbm=isch&sa=1&ei=o-vPXe69PM6YlwSx06DABA&q=catabolism+of+serotonin&oq=catabolism+of+serotonin&gs\\_l=img.3...51689.54844..55497...0.0..0.287.1902.0j8j3.....0....1..gws-wiz-img.....0i7i30.jxT7-MGc398&ved=0ahUKEwium9zq3e7IAhVOzlUKHbEpCEgQ4d6SGAc&uac=5](https://www.google.com/search?biw=1366&bih=637&tbm=isch&sa=1&ei=o-vPXe69PM6YlwSx06DABA&q=catabolism+of+serotonin&oq=catabolism+of+serotonin&gs_l=img.3...51689.54844..55497...0.0..0.287.1902.0j8j3.....0....1..gws-wiz-img.....0i7i30.jxT7-MGc398&ved=0ahUKEwium9zq3e7IAhVOzlUKHbEpCEgQ4d6SGAc&uac=5)

# Serotonin (5 hydroxytryptamine) functions

- Is a biologically active amine.
- Produced in:
  - \*CNS
  - \*Argentaffin cells of gastrointestinal tract
  - \*Platelets.

## Functions:

### 1- In CNS:

Acts as neurotransmitter.

- a- Regulate pain perception
- b- Regulation of sleep (relaxation) , reduce appetite
- c- Cognitive functions (learning) and improve mood (sense of well being & pleasure)
- d- Source of melatonin in the pineal body.

### 2-Stimulates smooth muscle contraction

→ Vasoconstriction so regulate temperature and blood pressure

### 3-Important for GIT motility.

**So deficiency causing insomnia, anxiety, weight gain, disability and depression**

# Clinical correlation

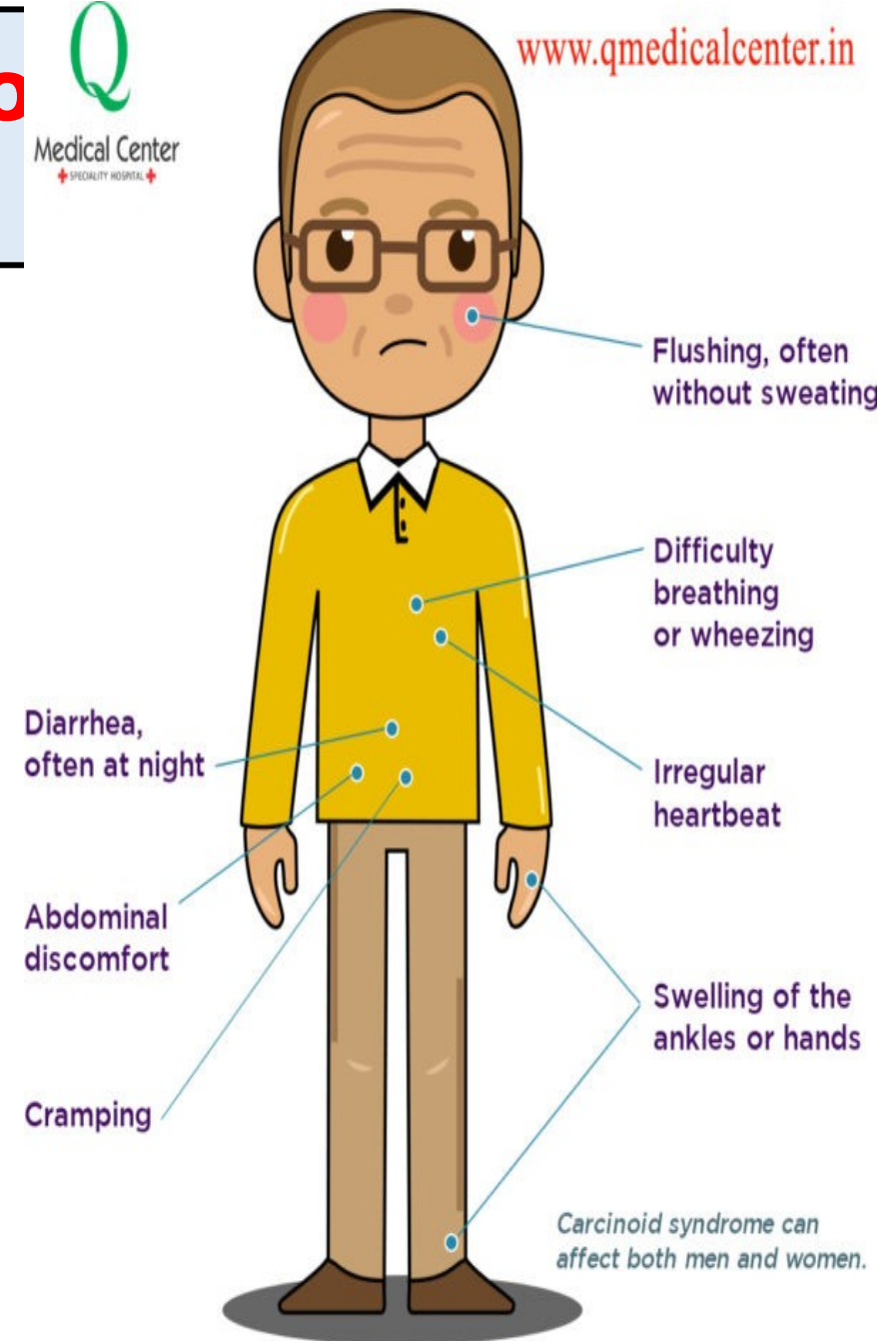
## 1- **Carcinoid tumor (argentaffinoma):**

- \* is a tumor of **argentaffin cells** of gastrointestinal tract
- \* characterized by:
- \* **increase** production of **serotonin**
- \* **decrease** production of nicotinic acid causing manifestations of pellagra  
( Diarrhea-Dementia &Dermatitis)
- \* and increase 5-HIAA in urine.

## 2-Selective serotonin reuptake inhibitors (SSRIs):

Maintain serotonin levels, thereby functioning as antidepressants

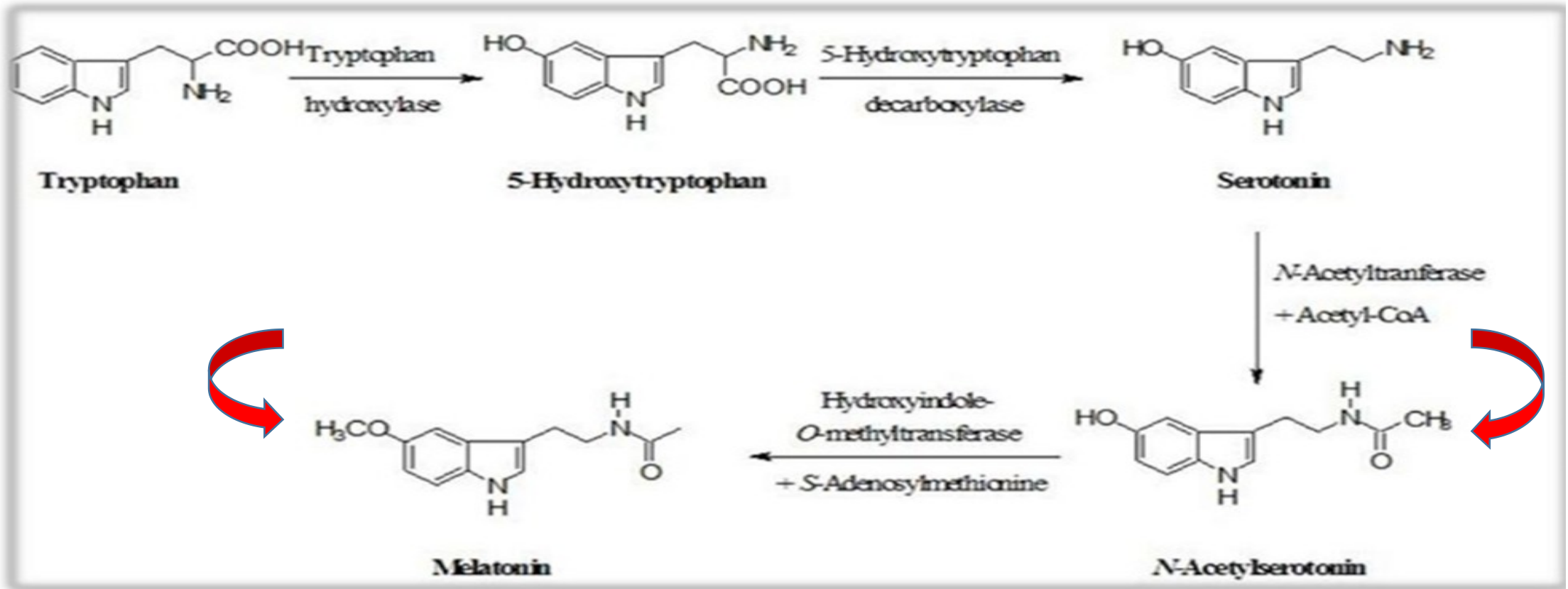
Like **Escitalopram** (sold under the brand name **Cipralex**)





# Melatonin

## *Synthesis of Melatonin*



# Melatonin Function

- Stimulate immune system
- Antioxidant protect against free radical
- Anticancer
- Its formation follows a circadian rhythm (diurnal variation); it is stimulated by dark and inhibited by light so regulate sleep cycle prevent insomnia so protect against Alzheimer

## *Melatonin And Age*

Some researchers also believe that melatonin levels may be related to aging. For example, young children have the highest levels of nighttime melatonin. Researchers believe these levels drop as we age. Some people think lower levels of melatonin may explain why some older adults have sleep problems and tend to go to bed and wake up earlier than when they were younger.



# Melatonin deficiency

1. Cigarettes
2. Caffeine
3. Frequent stress
4. Antidepressants

All previous due to lack of **sleep**

# Metabolism of neurotransmitters and related disorders (Quiz)



Serotonin (5HT): (True or false)

- 1- Is synthesized from tryptophan
- 2- Is found in platelets cells
- 3- Its degradative product is VMA

**Answer:**

1 (T)

2 (T)

3 (F)

## **2-Biologically active amines derived from phenylalanine and tyrosine:**

### **Catecholamines**

(**Catechol** means **benzene** ring with two **hydroxyl** side groups)\_

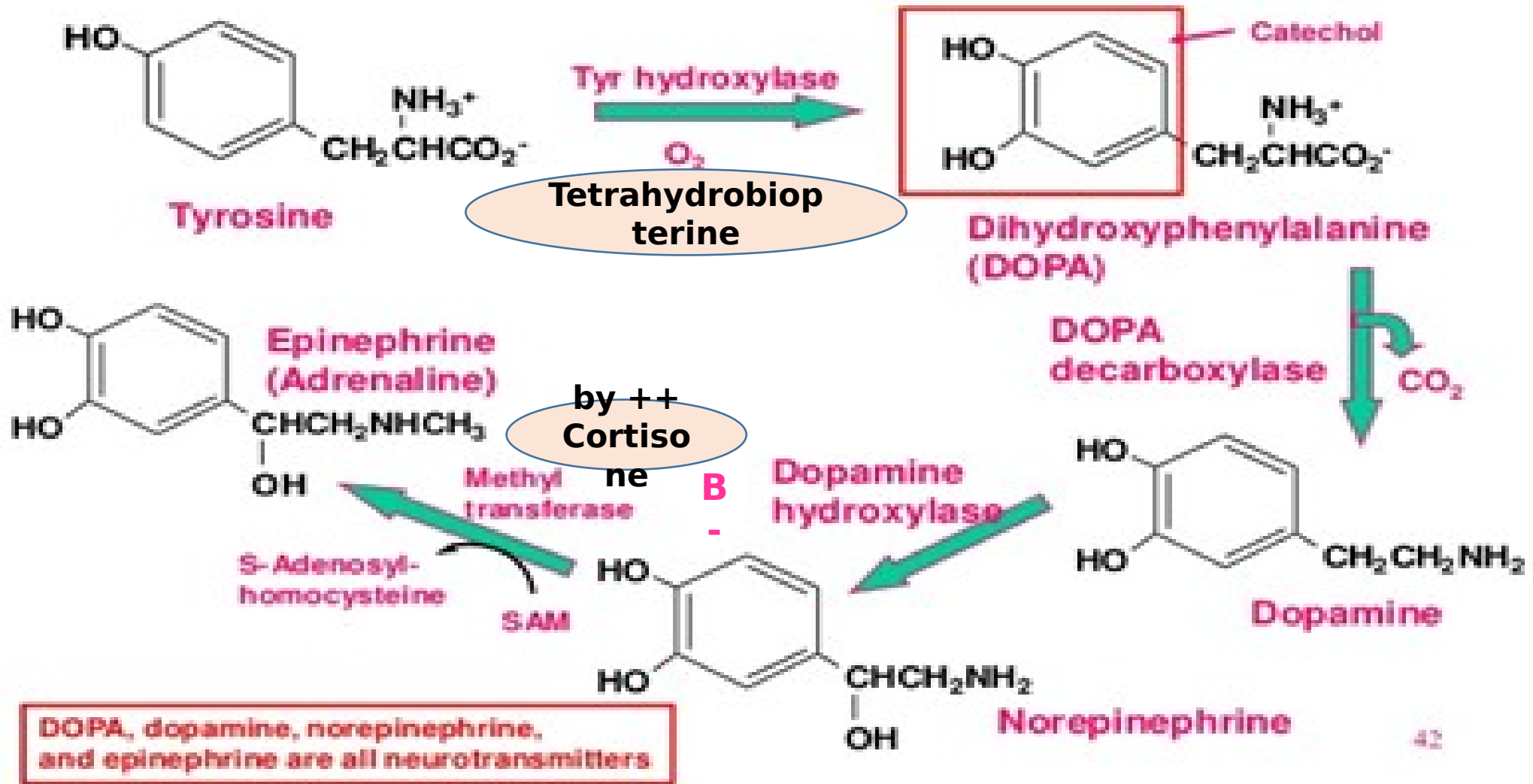
**\* Dopamine, Epinephrine and Norepinephrine**

**\* Are synthesized in the brain and adrenal medulla**

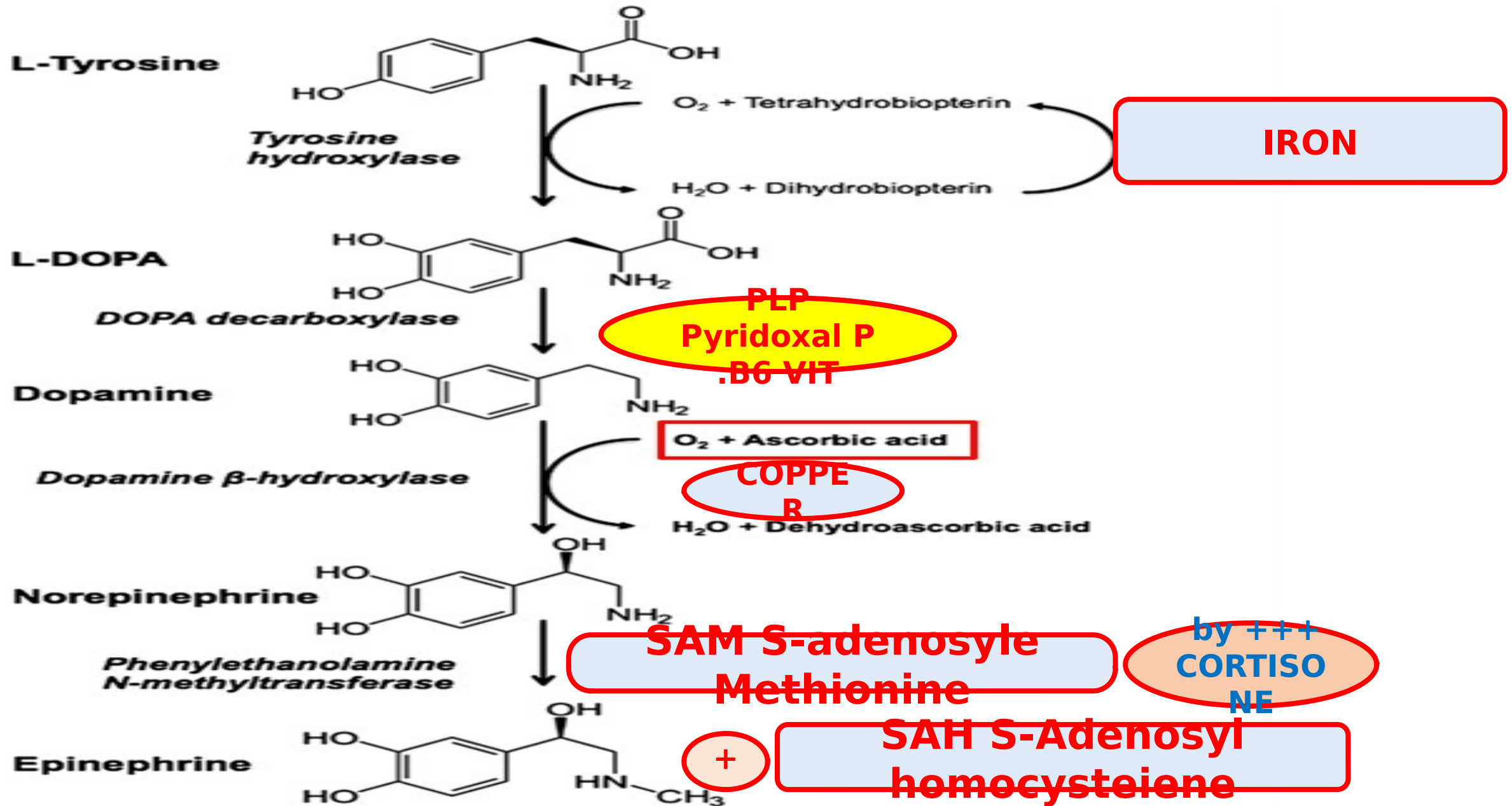
**(Chromaffin cells or pheochromocytes)**

**\* Release of the hormones epinephrine and norepinephrine from the adrenal medulla of the adrenal glands is part of the fight-or-flight response**

# Catecholamine Biosynthesis



# Vitamin C is required to synthesize catecholamines



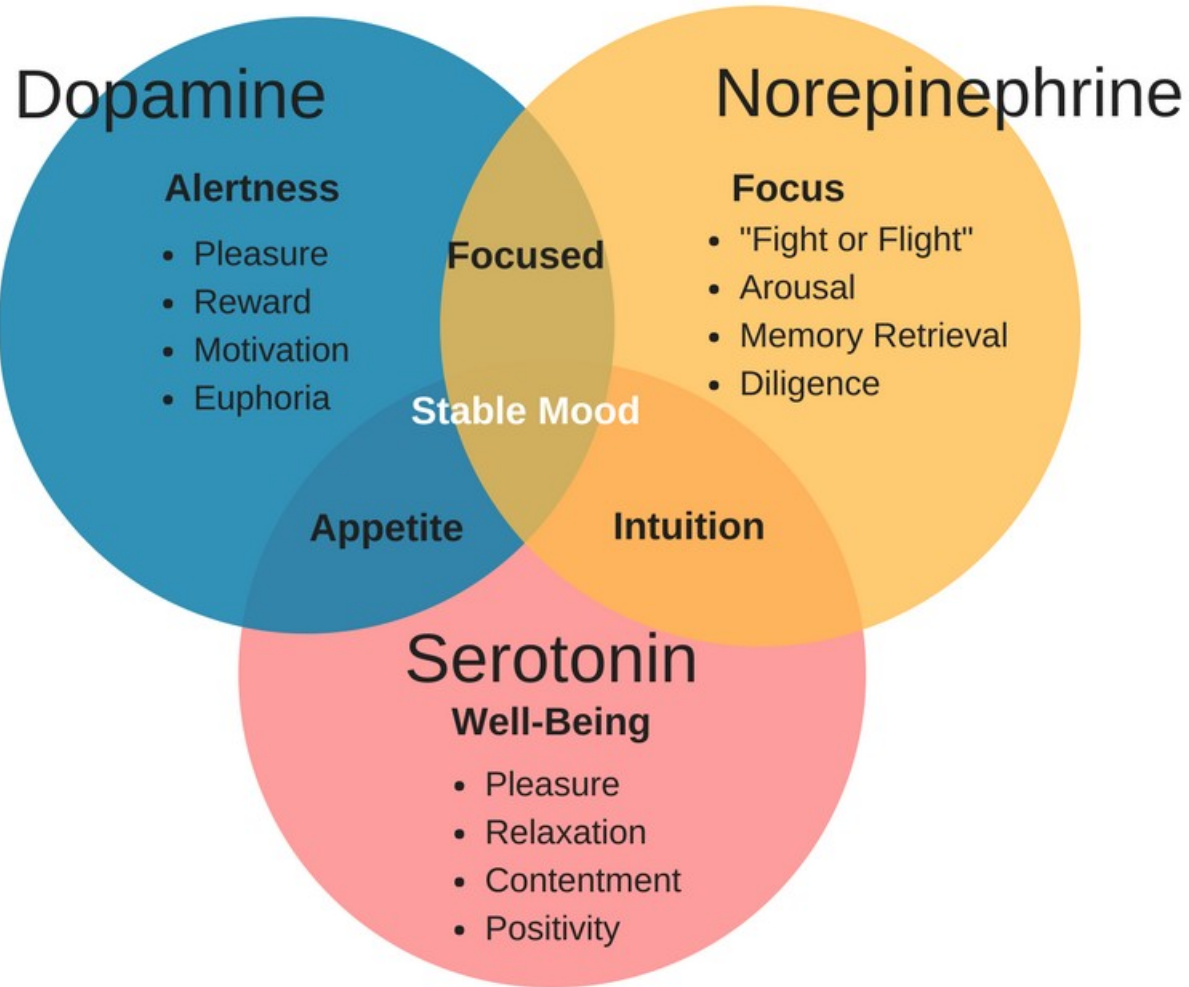
**The rate limiting enzyme in catecholamine synthesis is **tyrosine hydroxylase** which is inhibited by different catecholamines**

**(-ve feedback)**

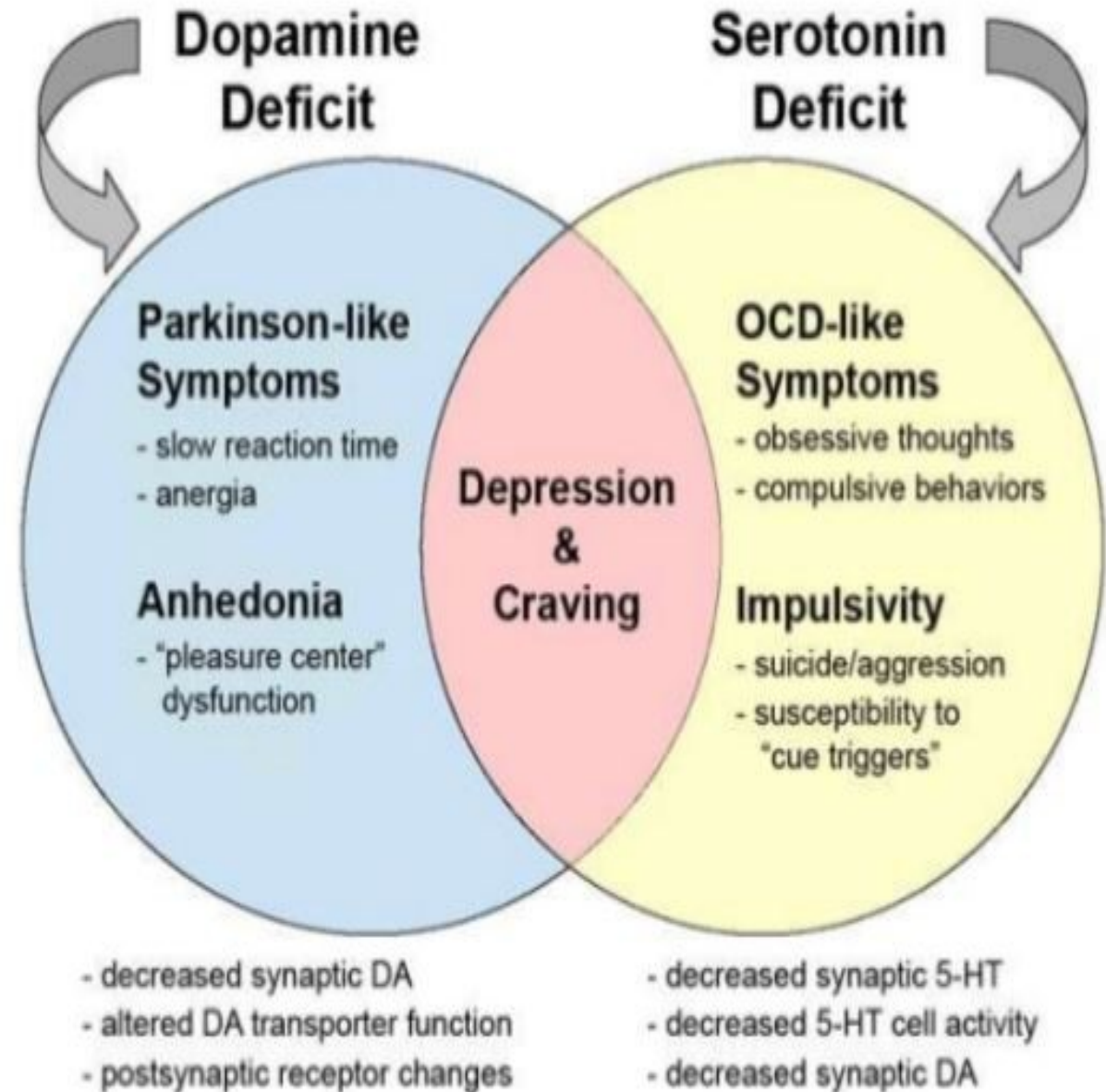
- **The primary end product in medulla is **NE** in Newborn**
- **With advancing of age Epinephrine is dramatically raised this depends upon **cortisol LEVEL which stimulate****
  - **N-methyltransferase enzyme**



# Function



# Deficiency

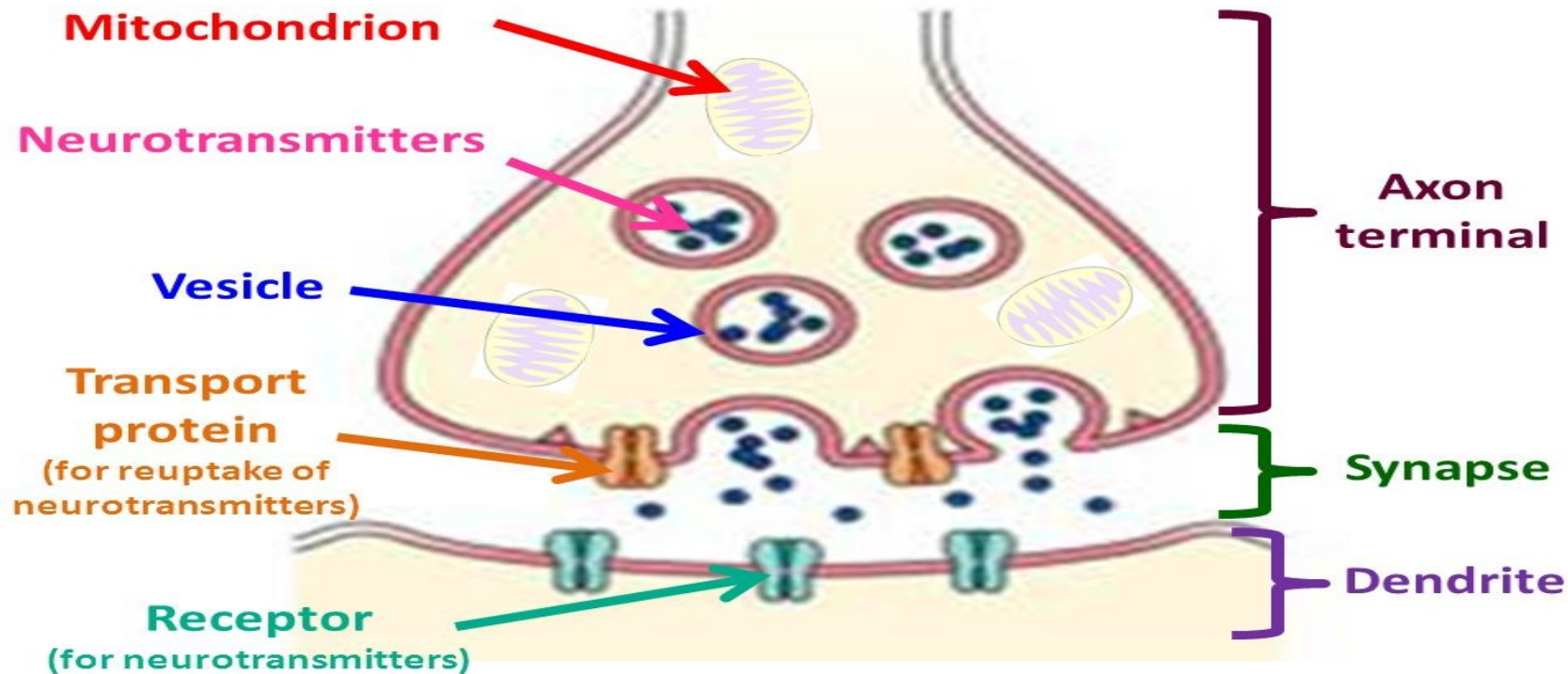


# Fates of catecholamines

## 1- Active uptake by sympathetic nerve endings:

It is  
cate

Label this diagram



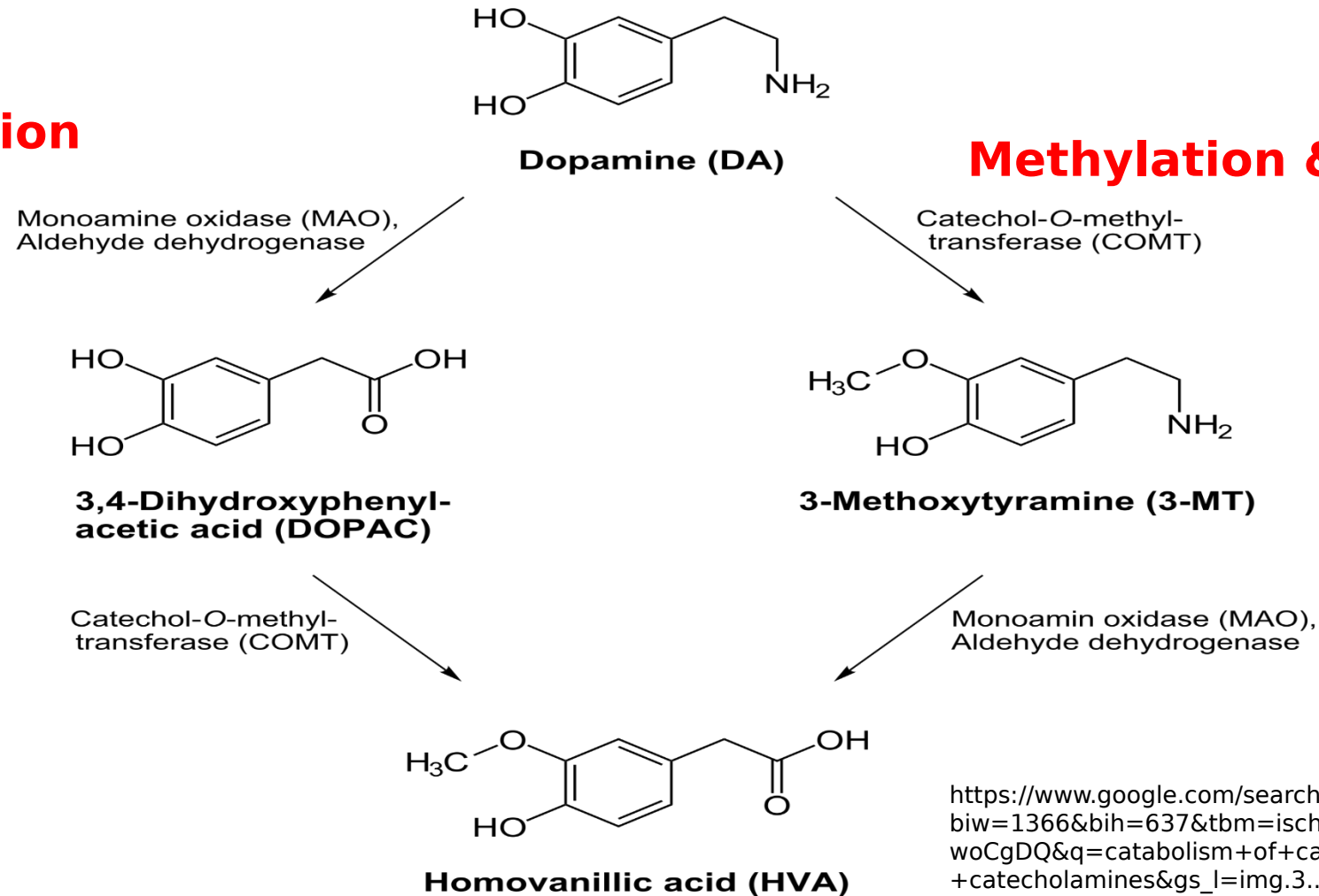
[https://www.google.com/search?biw=1366&bih=637&tbm=isch&sa=1&ei=GuzPXdLLH4j4U6HBv7AL&q=synthesis+of+catecholamines&oq=synthesis+of+catecholamines&gs\\_l=img.3..0j0i30.35582.39039..39822...0.0..1.345.2097.0j13j0i1..0..1.qws-wiz-](https://www.google.com/search?biw=1366&bih=637&tbm=isch&sa=1&ei=GuzPXdLLH4j4U6HBv7AL&q=synthesis+of+catecholamines&oq=synthesis+of+catecholamines&gs_l=img.3..0j0i30.35582.39039..39822...0.0..1.345.2097.0j13j0i1..0..1.qws-wiz-)

## 2- Catabolism to biologically inactive products:

### A) Catabolism of dopamine

#### Oxidative Deamination Inactivation &

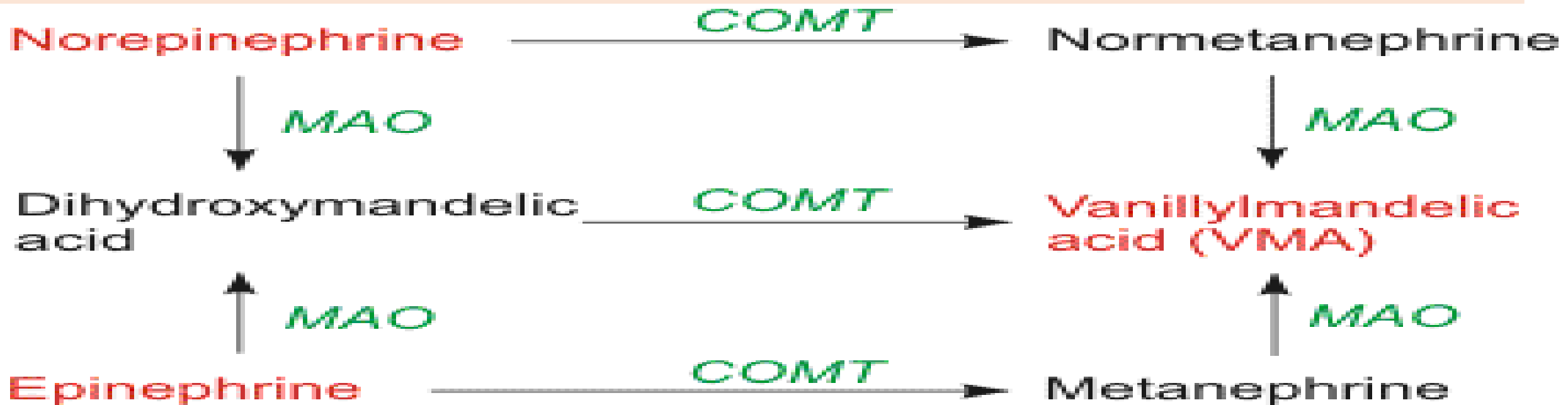
#### Methylation & inactivation



[https://www.google.com/search?biw=1366&bih=637&tbm=isch&sa=1&ei=Q-zPXd2sLay\\_lwS-woCgDQ&q=catabolism+of+catecholamines&oq=catabolism+of+catecholamines&gs\\_l=img.3..0i19.55442.58665..58920...0.0..0.197.1647.0j11.....0....1..gws-wiz-img.....0i7i30.\\_KwGe9sDZ-c&ved=0ahUKEwid2vK23u7IAhWs34UKHT4hANQQ4dUDCAc&uact=5](https://www.google.com/search?biw=1366&bih=637&tbm=isch&sa=1&ei=Q-zPXd2sLay_lwS-woCgDQ&q=catabolism+of+catecholamines&oq=catabolism+of+catecholamines&gs_l=img.3..0i19.55442.58665..58920...0.0..0.197.1647.0j11.....0....1..gws-wiz-img.....0i7i30._KwGe9sDZ-c&ved=0ahUKEwid2vK23u7IAhWs34UKHT4hANQQ4dUDCAc&uact=5)

## B) Catabolism of epinephrine and norepinephrine at adrenergic nerve endings

By MAO and COMT into **Vanillylmandelic acid (VMA)**  
The metabolic end product



MAO = monoamine oxidase  
COMT = catechol-O-methyltransferase

**\*VMA is detected in urine**

**The normal level of VMA in urine is 5 mg/day and is increased up to 500 \*  
.mg/day in Pheochromocytoma**

# Clinical Considerations

## Parkinson's Disease Symptoms

### 1- Parkinson disease:

- is a neurodegenerative disorder that affects predominately dopamine-producing (“dopaminergic”) neurons in a specific area of the brain called substantia nigra

### Treatment

- **L-dopa** ( precursor of dopamine ) is used in the treatment of parkinsonism as it can cross the blood brain barrier .... Dopamine cannot
- Also dopamine agonists LIKE **PARLODEL**
- **COMT INHIBITOR & MAO INHIBITORS** will increase dopamine concentration in brain v decreasing degradation

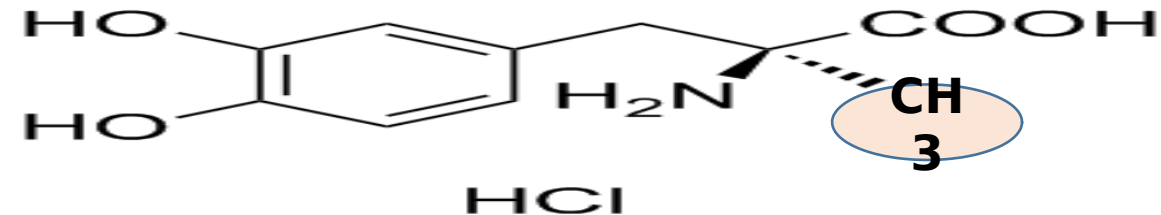


## 2. $\alpha$ -methyl dopa (Aldomet) :

Is used in the treatment of hypertension (a long-term medical condition in which the blood pressure in the arteries is persistently elevated)

$\alpha$ -methyl dopa can competitively inhibit DOPA decarboxylase as it is structurally similar to DOPA

DOPA will be converted into alpha-methyldopamine, a false precursor to norepinephrine, which in turn reduces synthesis of norepinephrine in the vesicles





# 3. Pheochromocytoma

\* is a rare, catecholamine-secreting tumor derived from **chromaffine cells** of adrenal medulla.

\* It is manifested by excessive production of catecholamines → severe refractory **hypertension, palpitation repeated several times.**

\* With much increase in **VMA LEVELS** in urine

\* **Treated** by **α-methyl tyrosine** which competes with tyrosine for tyrosine hydroxylase enzyme → inhibition of catecholamine synthesis.

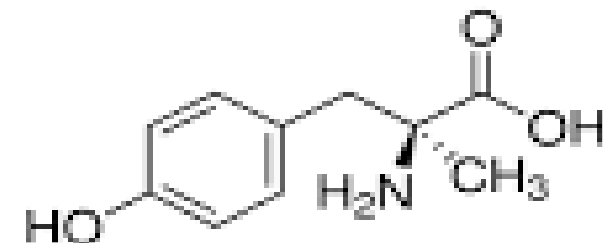
Pheochromocytoma: 3 most common symptoms

**"PHE**ochromocytoma"

- **P**alpitations
- **H**eadache
- **E**pisodic sweating (diaphoresis)

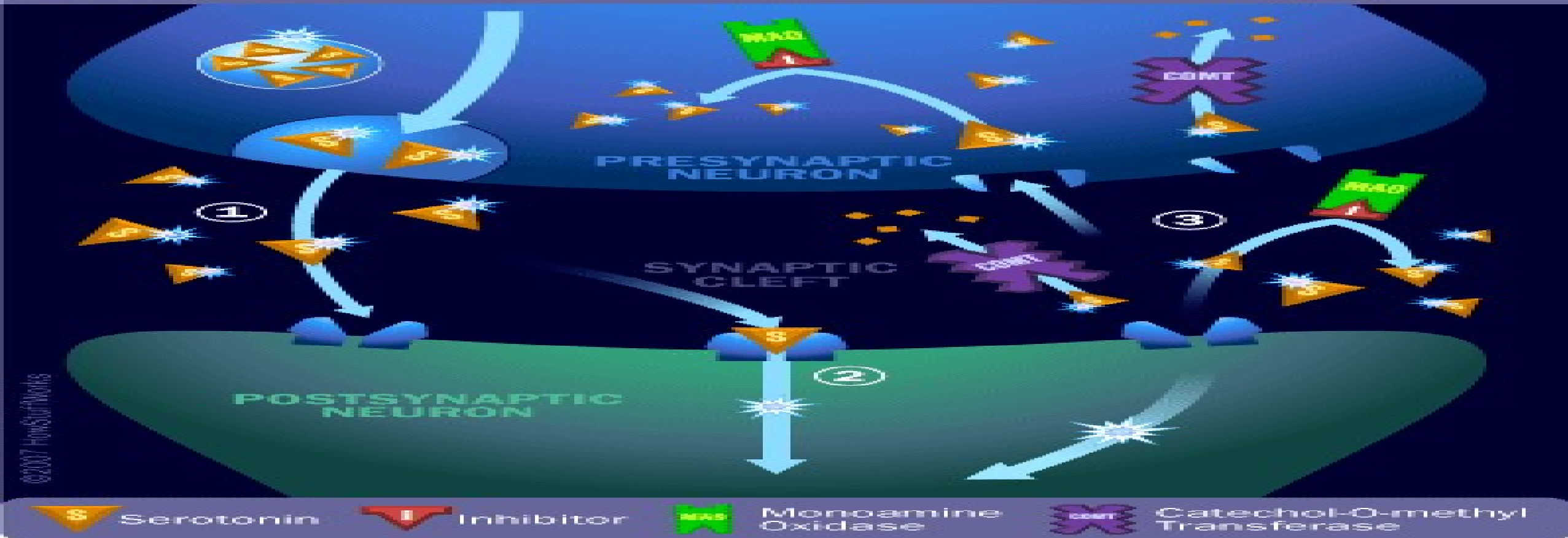


[www.medical-institution.com](http://www.medical-institution.com)



# 4. Monoamine oxidase inhibitors (MAOIs)

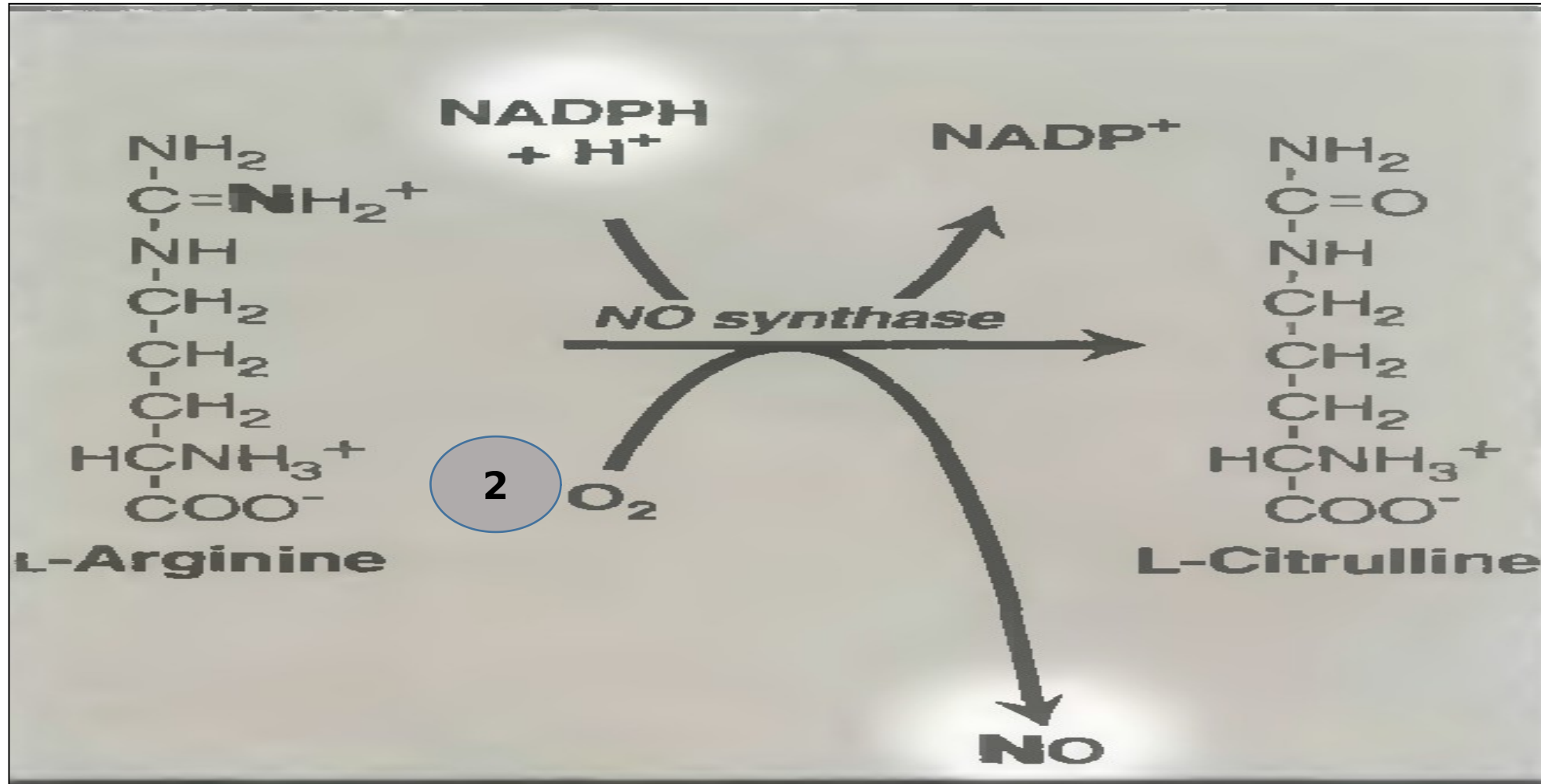
## How Antidepressants Work MAOI Inhibitors



- **MAOIs** block the actions of monoamine oxidase enzymes. **Monoamine oxidase enzymes** are responsible for breaking down neurotransmitters such as dopamine, norepinephrine, and serotonin in the brain
- **MAOIs** increase level of NE & Serotonin that is responsible for the **antidepressant** action of these drugs

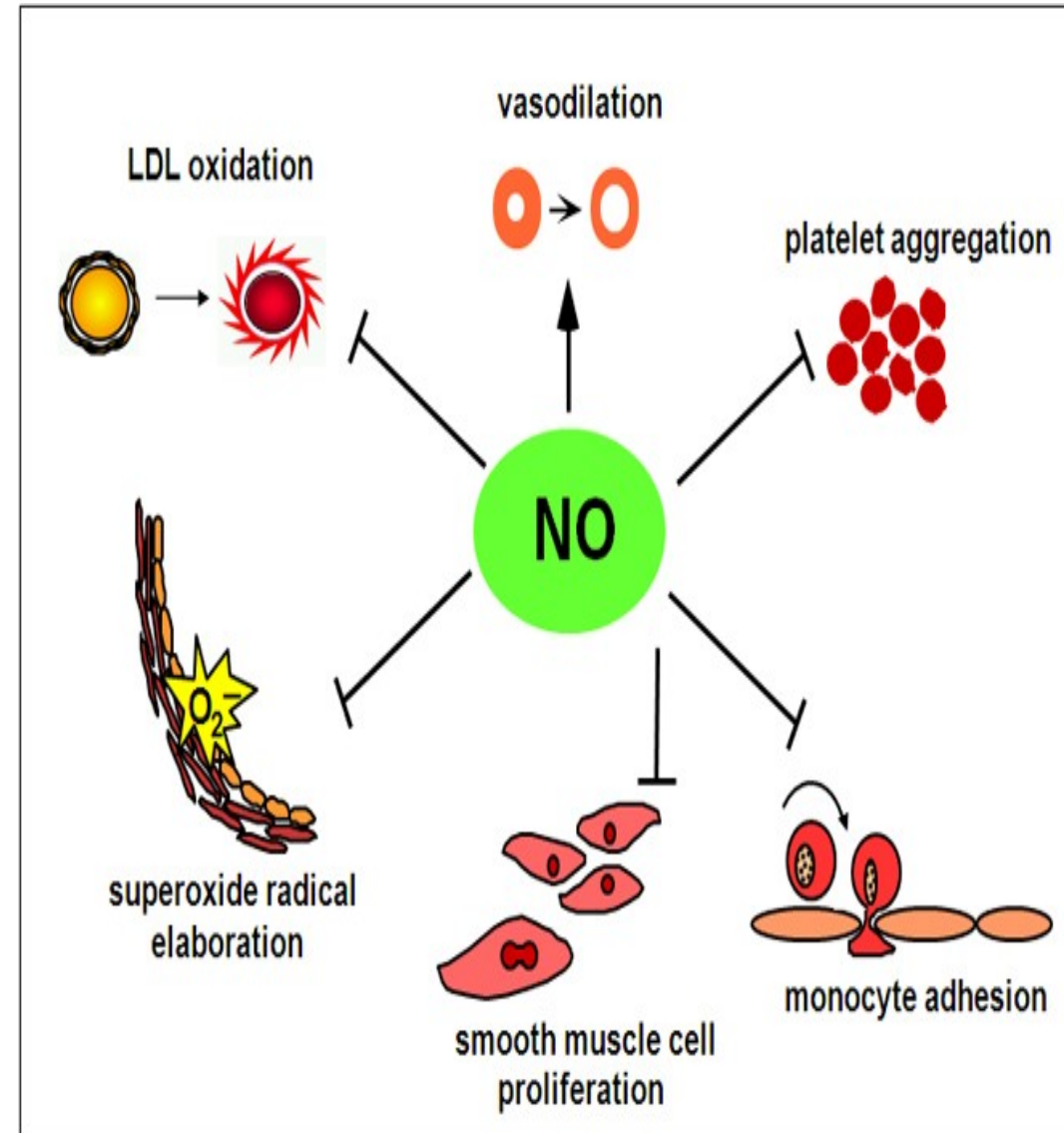


# Synthesis of nitric oxide ( NO )



# Functions of NO:

- Nitric Oxide is an endogenous protector of the vessel wall
- Is a potent **vasodilator** of cerebral, coronary and muscular arteries.
- It **relaxes** smooth muscles of GIT and urogenital tract so decreasing motility
- It **stimulates** release of hormones from hypothalamus.
- It is produced by



## **5- Pharmacological functions of NO:**

**Nitroglycerin( Dinitra) is used as tablet under -1  
tongue to treat angina, it gives NO causes VD  
so lowers blood pressure**

**Inhalation of NO can be used in the -2  
treatment of pulmonary hypertension and  
pulmonary edema via pulmonary  
Vasodilatation**

## Urogenital System

- Reninsecretion
- Penile erection
- Fertilization
- Spermatogenesis, oogenesis, ovulation



## Cardiovascular System

- Vasodilation
- Microvascular tone regulation
- Leukocyte adhesion
- Platelet aggregation/inhibition
- Microvascular permeability



## Respiratory System

- Bronchial dilation
- Pulmonary vascular reactivity
- Alveolar-capillary membrane permeability



**Nitric Oxide**  
physiological,  
biochemical, pathological  
functions

## Neurological System

- Learning
- Memory
- Neural protection
- Neuronal toxicity
- Neurotransmission
- Neuronal development
- Nociception



## Immune System

- Innate immunity
- Cytotoxic chemical
- Cellular injury protection
- Superoxide radical quenching



## Excretory System

- Glomerular filtration
- Renal vasodilation
- Renal endothelial function



## Endocrine System

- Posterior pituitary hormones
- gonadotropin hypothalamic releasing factor



## Vision

- Neurotransmitter within retina
- Regulation of retinal blood flow
- Visual transduction • Effector in photoreceptors
- Muscle tone in retinal and choroidal circulation



# **Gamma Amino Butyric Acid (GABA)**

**Is an**

**inhibitory neurotransmitter**

**derived from glutamic acid**

**by**

**glutamic acid decarboxylase (GAD) enzyme**

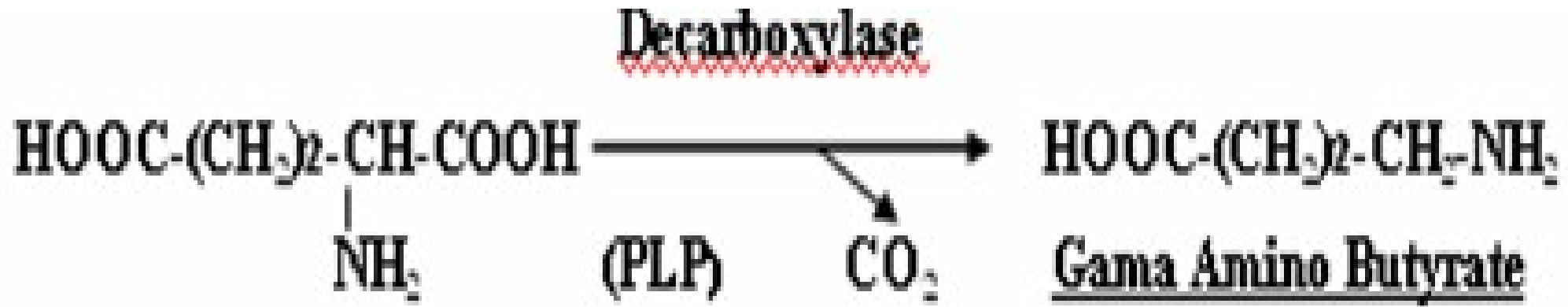
**pyridoxal phosphate is required as a coenzyme**



# Gamma Aminobutyric Acid (GABA)

- + GABA is the major inhibitory neurotransmitter of the brain.
- + It turns off the functions of the neurons.
- + It acts as a brake for the excitatory neurotransmitters that can cause anxiety.
- + Without GABA, brain cells would fire uncontrollably (as in epileptic seizures).
- + GABA deficiency is implicated in anxiety disorders, insomnia, and epilepsy.
- + GABA excess is implicated in memory loss and inability for new learning.
- + Agents that can block GABA-B receptors may improve learning and memory.

# Synthesis of neurotransmitter (GABA)



Glutamate

**Its level is reduced in brain in \***  
**Vitamin B6 deficiency with signs of**  
**hyperactivity and convulsions treated by**  
**Barbiturates ( GABA AGONIST)**

# **Metabolism of neurotransmitters and related disorders (Quiz)**

**A 56- year- old male presented with  
sever headache, palpitation,  
excessive sweating together with  
sever refractory hypertension  
repeated several times per week.**

**What investigation would you ask  
for to diagnose this case????**



# Metabolism of neurotransmitters and related disorders

## (Quiz)

**A 43- year- old man presents to the emergency room with chest pain . His blood pressure was 220/150 mmHg. Which of the following compounds might lower his blood pressure**

- ☒ a. Melanin
- b. Nitric oxide
- c. GABA
- d. Dopamine
- e. Serotonin

# Summary

## **1) Biosynthesis & degradation of Serotonin**

**Its relation to Depression & Carcinoid Tumor**

## **2) Biosynthesis & degradation of catecholamines**

**Its relation to:**

**\*Parkinson's disease**

**\*Hypertension & Pheochromocytoma**

**\*Depression**

## **3) Biosynthesis of GABA ..... Convulsions**

# Time for Students' Questions



# SUGGESTED TEXTBOOKS



- **Lippincott's illustrated reviews in Biochemistry by P.C. Champe, R.A. Harvey and D.R. Ferrier**
- **Fundamentals of Clinical Chemistry (Tietz)**
- **"Textbook of Biochemistry with Clinical Correlations" by T.M. Devlin**
- **"Harper's Biochemistry" by R.K. Murray, D.K. Granner, P.A. Mayes and V.W. Rodwell**

# Thank You

